

REMARKS

Status of the Claims

Claims 1-12 are pending. Claims 2, 3, and 7-12 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 1 and 4-6 are currently under consideration. Claims 1, 4, 6, 7, 9, 11, and 12 have been amended herein to more particularly point out the invention. Support for the amendments is found in the specification at least on page 5, lines 9-10, page 7, line 30- page 8, line 31; page 14, lines 1-19, and lines 31-32; page 19, lines 10-17; page 22, lines 25-29. No new matter has been added.

Indefiniteness Rejection Under 35 U.S.C. § 112

Claims 1 and 4-6 stand rejected under 35 U.S.C. § 112 second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action alleges that claims 1 and 4-6 are indefinite because they omit essential steps regarding where the enzyme and vector are administered. Without conceding the correctness of the rejection, and for the sole purpose of expediting prosecution, Applicants have amended claim 1 to recite that both are administered "to the subject." Claims 4-6 depend upon claim 1. Applicants believe this amendment obviates the rejection.

Written Description Rejection Under 35 U.S.C. § 112

Claims 1 and 4-6 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly failing to comply with the written description requirement. The Office alleges

that the specification only mentions α -galactosidase A for treating Fabry disease and thus concludes that administering a lysosomal hydrolase and a vector encoding a lysosomal hydrolase to treat Fabry disease is considered new matter. Applicants disagree with this conclusion. Nonetheless, in order to expedite prosecution applicants have amended claims 1, 4, and 6 to recite " α -galactosidase A." Claim 5 depends on claim 1. Accordingly, Applicants believe the rejection is obviated by this amendment.

Enablement Rejection Under 35 U.S.C. § 112

Claims 1 and 4-6 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly not enabled by the specification. The Office alleges that there is no evidence of record that the combination of gene therapy and enzyme replacement therapy using α -galactosidase A provide sufficient quantities of the enzyme at target cells in vivo to ameliorate the symptoms of Fabry disease in a patient. The Office further alleges that the claims are not enabled because the specification fails to provide adequate guidance and evidence regarding how to use any vector expressing any lysosomal hydrolase, including α -galactosidase A, for gene therapy in combination with any lysosomal hydrolase protein for enzyme replacement therapy. The Office concludes it would require undue experimentation for one skilled in the art to practice the full scope of the claimed invention. For the reasons set forth below, Applicants submit that this conclusion is incorrect.

A. The Standard For Enablement

"The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known

in the art without undue experimentation.” *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). “A patent need not teach and preferably omits what is well known in the art.” *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); MPEP § 2164.01. The Office bears the initial burden in establishing a reasonable basis to question enablement. MPEP §2164.04.

B. The Claimed Invention Is Enabled

The Office has maintained the rejection of claims 1 and 4-6 for alleged lack of enablement. In maintaining the rejection the Office has expressed concern regarding the unpredictability of the art and the scope of the claims. Applicants will address each of these concerns in turn.

1. Unpredictability of the Art

The Office alleges that the art of gene therapy and enzyme replacement therapy were unpredictable at the time of the invention and the “Achilles heel” of gene therapy was gene delivery. In support of its position the Office relied on Deonarain, 1998, *Expert Opin. Ther. Patents* 8:53; Verma et al., 1997, *Nature*: 389239; Eck et al., 1996 *Goodman & Gilman’s The Pharmacological Basis of Therapeutics*, p. 77-101 (McGraw Hill, New York); and Gorecki, 2001, *Expert Opin. Emerging Drugs* 6(2):187. The Office states that “combination therapy of gene therapy and enzyme replacement therapy has to be considered case by case, a successful gene therapy and enzyme therapy can not be extrapolated into success for another gene and enzyme therapies,” (page 5, Office Action, dated February 18, 2004). Applicants note that none of the references cited by the Office discuss the unpredictability of gene therapy in the context of Fabry disease,

thus nothing of record suggests the particular alleged unpredictability of treating Fabry disease with the claimed methods. More importantly, and as previously noted, the specification incorporates by reference U.S. Patent No. 6,066,626 ('626). The Office admits that the '626 patent demonstrates that a vector encoding biologically active human α -galactosidase A can be administered to an individual and the biologically active human α -galactosidase A can reduce GL3 levels in an animal model of Fabry disease (page 3, Office Action, dated February 18, 2004). Increased GL3 levels are the known result of the loss of enzyme activity and believed to be the cause of the symptoms cited by the Office (see, specification page 2, lines 5-23;). Moreover, measuring GL3 levels was an accepted method known in the art for measuring the efficacy of Fabry disease therapies (see, eg. Oshima et al., 1997, Proc. Natl. Acad. Sci. USA 5:2540 (Oshima); '626 patent) (both previously submitted) and is taught in the specification (page 22, lines 25-33). Applicants believe this demonstrates gene therapy is not unpredictable in the context of Fabry disease. No evidence of record suggests otherwise.

Regarding enzyme replacement therapy, Applicants note that while the Offices alleges it is unpredictable, the Office has provided no evidence of record to suggest this is the case. The Office is reminded of its burden in this regard (MPEP §2164.04). Moreover, enzyme replacement therapy for Fabry disease had been described in the art at the time of the invention (see, e.g., U.S. Patent No. 5,658,567)(courtesy copy enclosed). Applicants thus believe enzyme replacement therapy was not unpredictable at the time of the invention.

2. The Scope of the Claims

The Office objects to the term “treating” stating that treating “implies that the symptoms of the Fabry disease are ameliorated.” The Office lists a variety of symptoms associated with Fabry disease and concludes that there is no evidence of record that combining gene therapy and enzyme replacement therapy would provide sufficient α -galactosidase A to ameliorate the symptoms of Fabry disease in a patient. The Office has provided no evidence of record to support its implied definition of the term “treating.”

As discussed above the Office admits that the prior art demonstrated that vectors encoding α -galactosidase A could be administered and shown to decrease GL3 levels. Again, the record reflects that elevated GL3 levels cause the symptoms of the disease and measuring GL3 levels is an accepted method for evaluating therapies for this disease. Applicants believe the concerns regarding the term “treating” are unjustified when the claims are considered in light of the specification and knowledge in the art at the time of the invention.

The Office alleges that the specification fails to provide adequate guidance and evidence regarding how to use any vector expressing any lysosomal hydrolase, including, α -galactosidase A, for gene therapy in combination with any lysosomal hydrolase, including, α -galactosidase A for enzyme replacement therapy to treat Fabry disease via various administration routes to provide therapeutic effect in vivo. Applicants note that the claims, as amended, recite α -galactosidase A, not any lysosomal hydrolase. Moreover, the '626 patent discloses how to use both viral and non viral vectors to successfully lower GL3 levels in an accepted animal model for Fabry disease and the specification states that gene therapy may be administered

according to the '626 patent (page 23, lines 15-18). As stated above, elevated GL3 levels were known to be symptomatic of Fabry disease, and is an accepted marker of the disease. A skilled artisan reading the '626 patent in combination with the disclosure in the specification would be able to use viral and non-viral vectors to treat a subject with Fabry disease.

Enzyme replacement therapy has been described for Fabry disease (see '567) and is also taught in the specification. Moreover, the specification discloses both dosages and routes of administration for enzyme replacement therapy (see, e.g. page 23, lines 12-14; page 18, line 6-page 19, line 9). The specification also provides guidance regarding formulations for administering Fabry treatments to an individual (page 17, lines 28-36). Applicants believe that when the claims are considered in light of the specification and the art they are fully enabled. Accordingly, Applicants respectfully request withdrawal of the enablement rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge
any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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